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EDITORIAL COMMENT

Dismantling Mandates in the Treatment of Heart Failure*

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The Studies Of Left Ventricular Dysfunction (SOLVD) trial is a landmark study in the management of heart failure. The treatment limb of this trial (1) demonstrated unequivocally that long-term administration of the angiotensin-converting enzyme (ACE) inhibitor enalapril reduced mortality and hospitalization in patients with New York Heart Association functional class II and III heart failure on standard background therapy and thus, greatly extended the population base for proven ACE inhibitor benefit beyond that of the severe functional class IV patients studied in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial (2). The prevention limb of the SOLVD trial then also demonstrated ACE inhibitor benefit in patients with left ventricular (LV) systolic dysfunction with minimal to no symptoms (3).

See page 1825

Standard background therapy at the time (1980 to 1990) consisted of diuretic agents, digoxin, and in about 50% of patients, some type of vasodilator (nitrate, hydralazine, or calcium-channel blocker) (1). The results of the SOLVD trial, the CONSENSUS trial, and later, the Vasodilator-Heart Failure Trial (V-HeFT II) (4) provided the impetus to appropriately recommend that ACE inhibitors become a major component of background therapy in the management of all stages of LV systolic dysfunction and heart failure. A number of large controlled trials added patients with myocardial infarction as benefactors of chronic ACE inhibitor therapy (5–8).

The widespread application of ACE inhibitor therapy in heart failure became mired in the usual complex inertia of bringing trial-proven (evidence-based) treatments to clinical practice. Five years after U.S. Food and Drug Administration approval, ACE inhibitor utilization in heart failure was below 50%, and below 75% at 10 years, of an estimated 85% to 90% eligible patients with this condition; an astoundingly disappointing record in an era whose Paleolithic tools still consisted of diuretic agents, digoxin, and a few vasodilators. Various methods (e.g., review articles, conferences, guidelines) were used to promote ("get the word out") widespread use of ACE inhibitor in heart failure. One such tool was declaring ACE inhibitors as "mandated" therapy for heart failure. Although it is difficult to find this term in print, it became the routine part of the terminology (along with "paradigm shift") in all lectures and conferences addressing heart-failure management. Guidelines for managing LV systolic dysfunction and heart failure now uniformly include ACE inhibitors as the essential (and typically, the primary) component of standard background therapy for heart failure (9–11).

With the introduction and proven benefits of beta-adrenergic blockers and angiotensin receptor blockers (ARBs) in heart failure, do ACE inhibitors still merit their mandated position as standard background therapy, simply because these agents got there first? Certainly, the position of digoxin on the list of standard background therapies has faded somewhat, and ARB therapy has moved into equivalency with ACE inhibitors and, when properly dosed, has a better side-effect profile (12–14). As uncomfortable as it is when anything standard is threatened, should the sands of standard background therapy in heart failure be shifting?

Clinically experienced heart-failure specialists have known for decades that the optimal treatment plan for this condition is highly individualized; it is unlikely that any 2 of 100 patients, even at the same institution, will be receiving the same doses of the same medications. The same specialists have also had to deal with the clinical impression that certain patients with heart failure clinically respond better when beta-blockade is introduced before ACE inhibitors (or ARBs); for now, such patients include the euvolemic hyperadrenergic patient and most patients with chemotherapy-induced (doxorubicin, cyclophosphamide) cardiomyopathy (15). Even in these situations, it is often challenging to convince house staff and junior faculty, who are now expected to closely follow the mandated guidelines of their hospital or health maintenance organization, that it may be acceptable to start beta-blockade and advance its dose to optimal levels *before* adding the ACE inhibitor.

Although their opinions are rarely verbalized in public, many experienced heart-failure specialists likely believe that had beta-blockers (and ARBs) arrived at the scene first, ACE inhibitors would now be viewed as second-line agents or as optional add-on therapy for patients on the background therapy of beta-blockade, diuretic agents, spironolactone where indicated, probably an ARB, and perhaps digoxin. Herein lies the impact of the scientifically humble, yet piercing report in this issue of the *Journal* by Sliwa et al. (16) at the University of Witwatersrand, Johannesburg.

Sliwa et al. (16) found that certain clinical and laboratory responses were substantially better if beta-blockade (carvedilol) preceded, rather than followed, an ACE inhibitor (perindopril) in the initial sequence of the long-term (6 and 12 months) treatment plan of patients with New York Heart Association functional class II and III heart failure. The more favorable responses associated with starting with

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beta-blockade first include better functional class, higher achievable doses of beta-blocker drug, reduced diuretic-agent requirement, larger increment of LV ejection fraction by multigated angiography (nuclear), better echocardiographic parameters of diastolic function and reverse remodeling, and lower levels of plasma NT-pro-brain natriuretic peptide. In none of the measured end points did initiating ACE inhibitors first fare better than starting treatment with beta-blockade. And although some favorable responses were still achieved by adding an ACE inhibitor after six months of beta-blockade, the additional improvement for most of these parameters (e.g., LV ejection fraction, brain natriuretic peptide) was relatively modest in degree.

There are a number of possible scientific and theoretical reasons the results of this study make sense. Beta-blockade blunts the hyperactivation and effects of the major neuroendocrine forces in heart failure, namely the sympathetic nervous system and the renin-angiotensin-aldosterone system. The ACE inhibitors mostly affect the latter. Beta-blockade reduces heart rate to a far greater degree, with a consequent fall in myocardial oxygen consumption, while augmenting coronary perfusion by increasing diastolic time (17). Beta-blockade alone impedes the direct toxic effects on the myocardium of the elevated circulating catecholamines in heart failure. Beta-blockade consistently effects a better improvement in ejection fraction and reverse remodeling than that attained with chronic ACE inhibitor therapy. Achieving a higher dose of beta-blockade in the patients who were started on beta-blockers first (while both groups arrived at the same optimal ACE inhibitor dose) likely contributed to the more impressive response in this treatment group.

Most clinically experienced heart-failure specialists will not be surprised by the results of the Sliwa et al. study (16), and most should be pleased that this study was performed. Because of our preoccupation with ethics (often at the expense of science and, ironically in this case, the well-being of patients), it is unlikely that a similar study could have been performed in the U.S. In this "land of the free," we have unknowingly restricted our "freedom to choose" by mandating treatment and background therapies. It is reassuring to know that wisdom and rational thought remain intact beyond our borders.

Indeed, the Sliwa et al. study (16) has enormous limitations, most acknowledged by the authors. The drug, perindopril, does not jump to the front of one's mind when listing ACE inhibitor drugs, but it has been studied in heart failure with results that place this compound under the favorable class-effects of ACE inhibitors in this condition (18). Using other current trials as a guide, the study is small (total n = 78 patients) and it was performed at a single center. However, the study is adequately powered statistically for the end points selected. Blinding of treatment was limited to the examining physician (to assess functional class) and to those measuring end points. The study was not powered to address survival and other responses (e.g., exercise performance, dysrhythmias). In their favor, the investigators wisely excluded patients with heart failure secondary to coronary artery disease, who may have shown an even more favorable response to beta-blockade and thus would have been a complicating variable in the interpretation of the results. The study was supported by educational grants from Roche Pharmaceuticals and Servier Pharmaceuticals of South Africa. In South Africa, Boehringer Ingelheim is the marketing firm for carvedilol, and Servier performs the same role for perindopril.

Based on the results of the Sliwa et al. study (16), it is still not appropriate to conclude that the treatment plan for all patients with heart failure should now begin with a diuretic agent, beta-blockade, and in some instances spironolactone, with subsequent addition of an ACE inhibitor or ARB (and possibly digoxin). A large multicenter trial(s) incorporating the end points of survival and hospitalization would have to be performed to verify the results of the Sliwa et al. study (16), to determine the proper sequence of drug administration, and, in this era of polypharmacy, to define the necessary contributing components on the growing list of potentially beneficial medications. The Sliwa et al. study (16) could possibly provide the inspiration and impetus to launch such an investigation. Parenthetically, it is pleasing to see that some investigators are still willing to address important clinical and scientific questions outside the dominant multiyear, multicenter, and multithousand-patient trial.

Whether the ACE inhibitor will lose its coveted position as an obligatory component of background therapy for heart failure, or whether this question will ever be addressed again, remains to be seen. The results of the Sliwa et al. study (16) should certainly place this question in the minds of physicians treating this reasonably challenging, complex condition. In the least, the report should discourage the concept of "mandated" background therapy and replace it with "recommended" options. This shift will allow the delivery of better management to the individual patient and foster a more ideal population base for the development and study of newer therapies without being modified or masked by an entrenched, and perhaps less effective, therapy. Fortunately, combination hydralazine-nitrate was not mandated as an obligatory background therapy after the V-HeFT trial (19).

In contrast to most other disciplines dealing with complex, ill, and often end-stage patients (e.g., oncology, infectious diseases, nephrology), heart-failure specialists have been eager to mandate therapies. It is time to mature as a discipline and move beyond dogmatic declarations and mandates.

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